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A Rare Case of X-Linked Bulbo-Spinal Muscular Atrophy with Sensory Neuropathy and Tremors

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A RARE CASE OF X-LINKED BULBO-SPINAL MUSCULAR ATROPHY WITH SENSORY NEUROPATHY AND TREMORS

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ABSTRACT:
Kennedy disease (KD) is also known as spino bulbar muscular atrophy caused by a tandem C-A-G tri-nucleotide repeat. It is an adult-onset X-linked recessive inherited neurodegenerative disease involving lower motor neuron damage with predominance of facial muscles. It is often accompanied with androgen sensitivity, sensory nerve damage and endocrinal involvement. It has similar confusing symptoms and is often mis-diagnosed with most of the neuromuscular diseases like POEMS syndrome, myasthenia gravis, mitochondrial myopathy and amyotrophic lateral sclerosis. Hence clinical differentiation is important to prevent adverse outcomes and un-necessary treatment. Here we describe a rare case of a 46 year old Pakistani male who presented to us with progressive weakness and tingling of the limbs, bulbar symptoms, postural tremors and painful recurrent ulceration of the feet. Based on family history, clinical and electro diagnostic study he was diagnosed to have Kennedy disease. To the best of our knowledge, it is the first case report of Kennedy disease from Pakistan.

KEYWORDS: spino bulbar muscular atrophy, Kennedy disease, CAG repeat, X-linked recessive, POEMS syndrome

INTRODUCTION

In 1968 first report was published on an X-linked spinobulbar muscular atrophy and since the knowledge of its genetics in 1991 Kennedy disease (KD) has drawn attention of clinicians worldwide [1,2]. Its onset is mostly in the third decade of life and at approximately around 40 years of age with incidence rate of 1/100,000, the highest incidence being reported in the region of Wazard in Finland [3]. This disease manifests itself with lower motor-neuron damage clinically presenting with proximal as well as distal muscle weakness, muscular atrophy, cramps, sensory neuropathy, incomplete androgen insensitivity syndrome, endocrine involvement such as gynecomastia, impotence, testicular atrophy, metabolic changes, fine as well as postural tremors of hands, dysphagia, dysarthria, nasal voice and fasciculations particularly in the tongue [4]. Chewing is difficult due to fatigue and weakness of temporalis and masseter muscles with relative preservation of pterygoid muscles, but jaw drop can be seen [4]. Affected patients are always at a hazard of choking and aspiration-pneumonia due to involvement of bulbar muscles. It is caused by a tri-nucleotide CAG expansion and a mutation in exon 1 of the androgen receptor gene on the long arm of chromosome X (Xq 11-12) [5]. In comparison to other variants of motor neuron diseases, such as amyotrophic-lateral-sclerosis, progression in Kennedy is comparatively slower, with 2% decline in muscle power annually [6]. Some studies have shown that muscle decline in such patients is not only due to the involvement of motor-neurons but somewhat a primary myopathic-process is also involved [6]. Due to its over lapping features and clinical signs not being evident in the early course of the disease it is often confused with polyneuropathy, organomegaly, endocrine involvement, monoclonal gammopathies, and skin changes (POEMS syndrome), myasthenia gravis, mitochondrial myopathies, and amyotrophic lateral sclerosis. POEMS is a paraneoplastic disease due to plasma cell disorders. It is important for clinicians to have an acumen to differentiate Kennedy disease with all these orders. Here we describe a rare case of a 46 year old Pakistani male with progressive weakness and tingling of the limbs, bulbar symptoms, postural tremors and painful recurrent ulceration of the feet. To the best of our knowledge, it is the first case report of Kennedy disease from Pakistan.

CASE PRESENTATION:

A 46 year old Pakistani male presented to neurology out patient department with a history of adult insidious onset, gradually progressive, symmetrical weakness and tingling of upper as well as lower limbs for the past

6 years. This was followed by fine tremors in hands for 1.5 years and dysphagia, dysarthria, nasal regurgitation and a hot potato voice for the last 2 months. For the last 2 weeks he has developed tingling and twitching over extremities and face, cramps, fatiguability and loss of libido. Family history was significant in one of his brothers and maternal uncle whose disease was confirmed through NCS and EM G studies (Figure 1). He declined any past history of arthralgias, weight loss, photosensitivity, excessive urination or thirst. He belongs to a poor family and is a driver by profession having three children. He is a non smoker and non-addict. On physical examination his vital signs were normal, he had bilateral gynecomastia with bilateral postural tremors in hands, scanty pubic hair, and testicular atrophy (Figure 2). He had wasting of bilateral scapular and small muscles of hands with dysmorphic facial features including wasting of jaw muscles, weak articulation, bilateral facial muscle weakness with difficulty blowing air and whistling, atrophied tongue with fasciculations and palatal weakness (Figure 3). There was symmetrical weakness of proximal as well as distal muscles of upper and lower limbs, muscle strength was reduced, and tone was flaccid in all limbs . Reflexes were globally absent and had a mute planter. Jaw jerk and gag reflex were intact. There was no rigidity. He had a Medical Research Council sum-score of 50/60. Sensations to pin-prick were reduced in glove-stocking pattern distally in lower limbs with normal peri anal sensation and normal sense of position and vibration. Gait was high-steppage on straight walk. Abdominal, cardiovascular and chest examination revealed no abnormalities. Laboratory tests showed a normal blood profile and indices. Hepatic and renal functions, blood sugars and chest imaging showed no pathology. Serum levels of Vitamin-D, calcium and thyroid profiles were normal. Echocardiography and electrocardiogram were unremarkable. Lumbar puncture showed normal cell count and proteins. Repetitive nerve stimulation of (right median, ulnar, radial, Musculo cutaneous and facial nerve), anti-acetylcholine receptor antibodies and serum lactate levels showed no abnormality. Imagine of cervical spine showed no evidence of cord disease. Oral glucose-tolerance-test showed impaired glucose levels (levels of glucose in venous sample two hours post-prandial was 8.6mmol); triglycerides: 1.84mmol/L; lactic-acid: 3.4mmol/L; lactate-dehydrogenase (LDH): 156 IU/L; creatine-kinase levels were raised to (CK): 659 IU/L. Serum levels of estradiol were high (49.46 pg per ml) and prolactin was raised (27.69 ng per ml). Urine and serum protein electrophoresis showed no monoclonal antibodies. Nerve conduction study (NCS) of the limbs showed attenuation of ulnar, radial, tibial and peroneal nerve compound action potential amplitude while motor nerve conduction velocities were normal. The sensory potential amplitudes of the median and ulnar nerves were significantly attenuated. Superficial sural and peroneal nerve sensory potentials did not elicit response. 'F' waves obtained from stimulation of the ulnar and tibial nerve appeared lower than 50%. Electromyography (EMG) study was neuropathic with findings suggestive of both active and chronic denervation and reinnervation in a diffuse distribution including upper/ lower limbs, thoracic paraspinals and the genioglossus muscles. Muscle biopsy of the left quadriceps showed signs of chronic denervation marked predominance of type I muscle fibers with variable and diffuse non specific changes. Sural nerve biopsy showed loss of large diameter myelinated axons Genetic testing could not be done due to non-availability and financial constraints of the patient. On the basis of his typical clinical findings, positive family history and multi system involvement beyond just the motor neurons he was diagnosed to have Kennedy disease. He was started on symptomatic treatment with propranolol at 80mg/day to control his tremors along with physiotherapy, speech therapy and facial muscle exercises as the main stay of treatment. Life style modification was advised for new onset mild diabetes with monitoring of glucose levels. Daily dressing, hydration of skin and foot care was advised for sensory ulcerations. Patient and his family was counseled regarding prognosis and an endocrinologist was taken on board for further management.

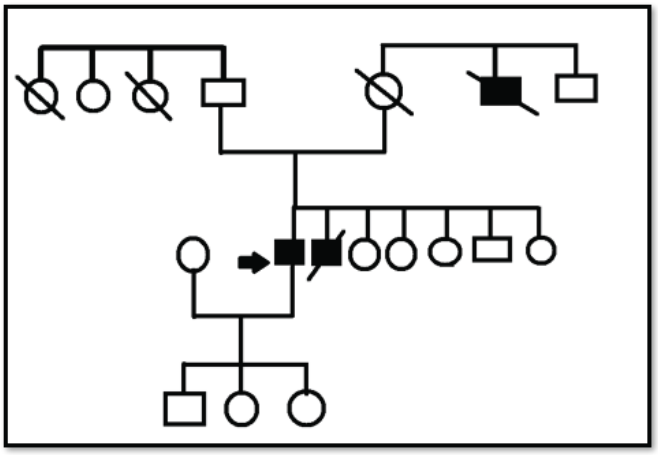

Figure 1: Family pedigree showing X-linked inheritance

Figure 2: Bilateral gynecomastia and facial muscle wasting

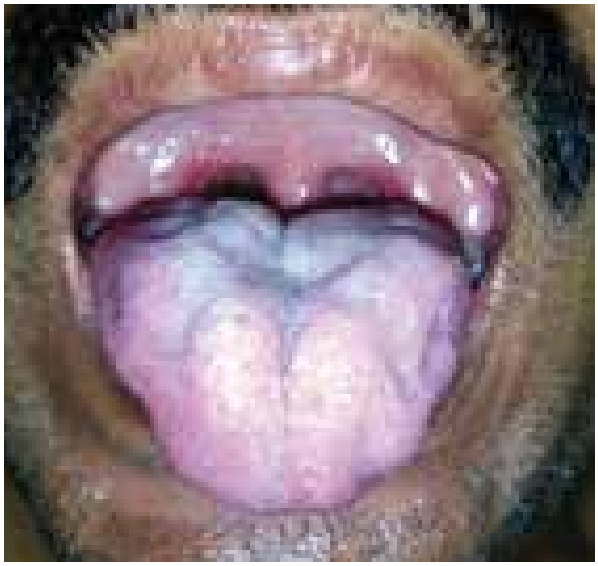

Figure 3: Tongue atrophy

DISCUSSION:

Kennedy disease must be clinically differentiated from other varieties of spinal muscular atrophy, hereditary sensory and motor polyneuropathies, myasthenia gravis, POEMS syndrome and amyotrophic lateral sclerosis. The main differentiating points are the patterns of inheritance, family history and the typical clinical features due to endocrinopathies [7]. During the early course of the disease, it might be very difficult to diagnose on the basis of early symptoms like muscle cramping and easy fatiguability leading to mis diagnosis of myasthenia gravis, early motor neuron disease, amyotrophic lateral sclerosis, limb-girdle or facio-scapulo-humeral muscular dystrophies or hereditary neuropathies [8]. In our patient cervical-cord disease, myasthenia-gravis, POEMS syndrome and mitochondrial-myopathies were excluded together with comprehensive clinical history, strong familial history, typical clinical features, and the laboratory results. He had postural tremors, facial muscle involvement, bulbar signs, impaired glucose tolerance test, abnormal breast development, loss of libido and testicular atrophy along with electrodiagnostic studies which all favored the diagnosis of Kennedy disease rather than immune-mediated polyneuropathies or gammopathies. The only limitation in our case was the genetic testing which could not be done due to financial constraints, limited resources of the family and non availability of genetic testing in our country. Tremors have been rarely described in neuronopathies but may not be uncommon accounting for about 40% of patients developing postural tremors or head tremors later in life as in Kennedy disease [9]. Sensory neuropathy with abnormal evoked potentials on electro diagnostic studies is not un-usual in Kennedy disease and must not be confused with any alternative diagnosis like acquire or immune mediated demyelinating polyneuropathies [10]. Currently no cure has been found for Kennedy disease and the goal is to treat symptomatically with physiotherapy and rehabilitation as the main stay to slow down muscle atrophy. Since this disease shows androgen-dependent pathophysiology therefore by inhibiting the action of androgens using a 5 alpha-reductase inhibitor dutasteride can be fruitful to halt progression of neuro degeneration in such patients but proven clinical trials have not been published [11]. Due to its atypical clinical features, misdiagnosis is common in Kennedy disease causing inappropriate treatment. This not only increases economic burden on patients and their families but also increases psychological impact on patient's mind.

CONCLUSION: It is important to differentiate Kennedy disease from other neuromuscular disorders as many disorders of varying severity and outcomes show close resemblance. Due to its atypical clinical features, misdiagnosis is common in Kennedy disease causing inappropriate treatment. This not only increases economic burden on patients and their families but also increases psychological impact on patient's mind. Co-existing sensory neuropathy also requires prompt patient education to prevent recurrent painful ulcerations and limb amputation.

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Zakir Jan; manuscript writing, manuscript review
Tehmina Inayat; data analysis, manuscript writing, manuscript review
Mazhar Badshah; data analysis, manuscript review
Muhammad Irshad; data analysis, manuscript writing, manuscript review